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TRANSMITTAL FORM

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First Named Inventor	Sawada, Toyohiro, et. al.
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Examiner Name	Unassigned
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ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Response
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  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
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- ☒ Certified Copy of Priority Document(s)
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- ☐ Assignment Papers *(for an Application)*
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- ☐ Licensing-related Papers
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

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Signature	Joseph R. Snyder
Date	May 17, 2001

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PATENT
Attorney Docket No.: 019941-000510US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Toyohiro Sawada et al.

Application No.: 09/834,410

Filed: April 12, 2001

For: TIMED-RELEASE COMPRESSION-COATED SOLID COMPOSITION FOR ORAL ADMINISTRATION

Examiner: Unassigned

Art Unit: Unassigned

COMMUNICATION UNDER 37 CFR §1.78(5)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith a Certified Copy of an English translation of their Priority Document, i.e., U.S. Provisional Application No. 60/198,086, for the above-referenced application.

Respectfully submitted,

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CERTIFICATION OF TRANSLATION

This is to certify ~~that the~~ attached Japanese to English translation has been proofread and edited by a qualified professional translator competent in both languages, and is an accurate and complete rendering of the content of the original document to the best of our ability. The following document is included in this certification, Specification of "Oral Pharmaceutical Compositions For Reducing Drug-Interaction In Phamacotherapy And Method Thereof".

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SPECIFICATION

ORAL PHARMACEUTICAL COMPOSITIONS FOR REDUCING DRUG-INTERACTION IN PHARMACOTHERAPY AND METHOD THEREOF

Technical Field

The present invention pertains to an oral pharmaceutical preparation with which drug interaction with other concomitant drugs is reduced and a method thereof. In detail, the present invention pertains to an oral pharmaceutical preparation with which undesirable interaction between other concomitant drugs and drugs that use the same route in terms of absorption, distribution, metabolism or excretion is reduced and a method thereof.

Background Art

Today drugs are rarely used singularly as a result of diversification of medicine and changes in patient phase with aging, and in many cases multiple drugs are administered simultaneously or at staggered administration times. In this case, interaction between drugs that are administered concomitantly sometimes occurs. Interaction between the drugs in question is classified as pharmacodynamic drug interaction, whereby there is a change in sensitivity, etc., to the drug at its site of action, and pharmacokinetic drug interaction, where there is a change in the *in vivo* kinetics of the drug. With respect to the former, interaction by concomitant use can be estimated if the clinical mode of action of the drugs is known, and the fact of the matter is that the actual results of concomitant therapy are improved using this same interaction. However, with respect to the latter, clinically, the *in vivo* kinetics of a drug is still unknown and even when it is known, unexpected results occur when drugs are combined ("Clinical Pharmacokinetics, Revised Version 2," Chapter VII: Drug Interaction, page 107, Ryuichi Kato, author, Nankodo Publishing).

Pharmacokinetic drug interaction almost always develops because the drugs themselves compete for one route (enzymes, carriers, etc.) when drugs that use the same routes in terms of drugs absorption, distribution, metabolism or excretion are used concomitantly.

This type of pharmacokinetic drug interaction is undesirable unless it is used for an additive action or synergism. The method has been adopted for averting concomitant use of drugs that interact with one another when a prescription is written by a physician or pharmacist whereby attention is drawn to "Drug Safety Data" presented by the Ministry of Health and Welfare and the column on precautions for concomitant use contained in the attached drug literature.

Moreover, the claim is presented in "Drug Prediction Manual," (Yasufumi Sawada, author; Yakugyo Jiho Publishers) that it is possible to avert interaction with an administration protocol whereby the administration time of concomitant drugs to a patient is staggered. However, the administration time is precisely specified and the protocol

calls for administration of as much as 6 to 7 times/day with concomitant use of metal cation-containing antacids (magnesium, aluminum, etc.) and new quinolones (norfloxacin, etc.), which were used as examples in this text, and in view of patient compliance, this protocol cannot realistically be used.

Consequently, even if from a pharmacological standpoint the drugs themselves realize excellent therapeutic results when used concomitantly, concomitant use has been averted in the past because of drug interaction and satisfactory therapeutic results could not be realized.

Moreover, since pharmacokinetic interaction with drugs is induced by some foods, pharmacists give instructions on how to take drugs explaining precautions when drugs are taken. However, this has become a source of reduced patient compliance.

That is, the purpose of the present invention is to present an oral pharmaceutical preparation with which drug interaction due to competition for drug metabolism by cytochrome P450, particularly drug metabolism by CYP3A4, in the upper small intestine, such as the duodenum, jejunum, etc., and/or liver in the presence of other concomitant drugs is reduced and a method thereof.

Disclosure of the Invention

Under these circumstances, the inventors hypothesized that it might be possible to reduce competition for metabolism in the epithelial cells of the small intestine, or to vary the time for which drugs that have been absorbed *in vivo* (intravascularly) coexist with concomitant drugs in the liver, and thereby reduce drug interaction between drugs and concomitant drugs, by releasing drugs from a preparation after a specific time lag in order to vary the time for which concomitant drugs and drugs coexist in the epithelial cells of the small intestine (site of metabolism by CYP3A4) (time control) and/or by making a phamaceutical preparation move to the lower small intestine, such as the ileum, etc., or the colon, where there is little CYP3A4, and releasing the drugs from the preparation at this site while concomitant drugs are being metabolized in the upper small intestine, such as the duodenum, jejunum, etc., where there is a considerable amount of CYP3A4, so that the site of absorption of the drugs and the concomitant drugs is varied (site control). Thereupon, the inventors conducted intense studies of timed-release preparations and successfully completed the present invention upon discovering that even when drugs are simultaneously administered with concomitant drugs with which there is drug interaction over CYP3A4, changes in the blood concentration of the concomitant drugs can be controlled by using tablets with a core that are made by compression molding of a combination of a hydrophilic base and hydrogel-forming polymer substance with a core containing a drug. That is, the present invention pertains to an oral pharmaceutical preparation, which contains a core containing a drug, a hydrophilic base, and a hydrogel-forming polymer substance. Moreover, the present invention pertains to an oral pharmaceutical preparation containing a core, which contains a drug and a dissolving filler, a hydrogen base, and a hydrogel-forming polymer substance. The present invention further pertains to a method of reducing drug interaction between concomitant drugs and drugs that use the same route in terms of absorption, distribution, metabolism, or

excretion by using an oral pharmaceutical preparation, which contains a core containing a drug, a hydrophilic base, and a hydrogel-forming polymer substance.

The oral pharmaceutical preparation and method thereof of the present invention will now be explained in detail.

In the present invention the term drug interaction means pharmacokinetic drug interaction, in other words, drug interaction between multiple drugs that use the same route in terms of drug absorption, distribution, metabolism, or excretion. Specific interaction is discussed below:

(a) Interaction in terms of drug metabolism

Drugs are deactivated or converted to water-soluble metabolites that are readily excreted via the kidneys by the effects of drug-metabolizing enzymes in the liver. Cytochrome P450 (CYP) is said to be the most important drug-metabolizing enzyme. It is said that approximately 70% of pharmacokinetic drug interaction is around drug metabolism, and of this, 95% or more is interaction via CYP. Many molecular species of CYP exist, and those that play the most important role in drug metabolism are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The molecular species of CYP involved in drug metabolism is determined by the chemical structure of the drug. Moreover, the molecular species of CYP involved in metabolism varies with each site in the chemical structure, and there are also drugs that are metabolized by multiple molecular species of CYP.

Theophylline, caffeine, phenacetin, clomipramine, imipramine, fluvoxamine, zolpidem, clozapine, proprapanolol, propafenone, chlorzoxazone, tacrine, acetaminophen, ondansterone, verapamil, etc., are drugs that are metabolized by CYP1A2 and/or drugs that inhibit CYP1A2.

Diclofenac, naproxen, ibuprofen, piroxicam, flurbiprofen, indomethacin, phenytoin, carbamazepin, tolbutamide, glibenclamide, glipizide, glimepiride, warfarin, losartan, torsemide, dronabinol, tenoxicam, mefanamic acid, sulfafenazole, etc., are drugs that are metabolized by CYP2C9 and/or drugs that inhibit CYP2C9.

Mephenytoin, diazepam, phenytoin, phenobarbital, hexobarbital, mephobarbital, omeprazole, lansoprazole, proguanil, amitriptyline, clomipramine, imipramine, sitalopram, propranolol, thiridazine, carisoprodol, warfarin, nirvanol, etc., are drugs metabolized by CYP2C19 and/or drugs that inhibit CYP2C19.

Propafenone, flekainid, mexiletine, enkainid, spartein, N-propylazimalin*, metoprolol, timolol, pindolol, propranolol, bufuralol, perbutolol, popindolol, alprenolol, carbedilol, debrisokin, indolamine, guanoxan, urapidil, nisergolin*, risperidone, thioridazine, perphenazine, clozapine, trifluperiol*, fluphenazine, chlorpromazine, haloperidol, clomipramine, nortriptyline, amitriptyline, imipramine, trimipramine, desipramine, zolpidem, brofalomin*, amiframine*, paroxetine, fluoxetine, maprotiline, banrafaxin*, fluvoxamin, trazadone, tomoxetin*, dihydrocodeine, oxycodeine, codeine, tramadol, dextromethorphan, femformine, perhexelin, chlomiopran, quinidine, cimetidine, ondansteron, etc., are drugs that are metabolized by CYP2D6 and/or drugs

that inhibit CYP2D6. [Translator's note: * indicates transliteration of phonetic characters]

Anfentanyl*, fentanyl, sulfentanyl, cocaine, dihydrocodeine, oxycodeine, tramadol, erythromycin, clarithromycin, troleandomycin, azithromycin, itraconazole, ketoconazole, dapsone, midazolam, triazolam, alprazolam, diazepam, zolpidem, felodipine, nifedipine, nitrendipine, amlodipine, isradipine, nicardipine, nimodipine, nisoldipine, nildipine, bepridil, diltiazem, verapamil, astemizole, terfenadine, loratidine, cyclosporine, tacrolimus, rapamycin, amiodarone, disopyramide, lidocaine, propafenone, quinidine, imipramine, amitriptyline, clomipramine, nafazodone, sertraline, trazodone, haloperidol, pimozide, carbamazepine, ethosuximide, trimethadione, simvastatin, lovastatin, fluvastatin, atrovastatin, etoposide, ifosfamide, paclitaxel, tamoxifen, taxol, vinblastine, vincristine, indinavir, ritonavir, saquinavir, testosterone, prednisolone, methylprednisolone, dexamethasone, proguanil, warfarin, finasteride, flutamide, ondansteron, zatosetron, cisapride, cortisol, zonisamide, desmethyldiazepam, conivaptan*, etc., are drugs that are metabolized by CYP3A4 and/or drugs that inhibit CYP3A4 (Sogo Rinsho, 48(6), 1427-1431, 1999/ Seishinka Chiryogaku, 14(9), 951-960, 1999). [Translator's note: * indicates transliteration of phonetic characters]

It appears that when multiple drugs that are metabolized by CYP and/or inhibit CYP of the same molecular species in this way compete for these metabolizing enzymes, the extent of this same competition varies with the affinity of the drug for the CYP, but metabolism will be inhibited in some way. Metabolism of drugs that have poorer affinity for the CYP will be inhibited and as a result, there will be drug interaction in the form of elevated blood concentration, prolonged blood half-life, etc.

For instance, inhibited metabolism, resulting in a rise in the blood concentration, of midazolam and terfenadine, cyclosporine, etc., by erythromycin, of methyl prednisolone by ketoconazole, and of lovastatin by itraconazole are examples of concomitant use of drugs that inhibits metabolism by CYP3A4.

Moreover, there are cases where foods that are metabolized by the same species of CYP as drugs compete for the same metabolizing enzymes to inhibit in some way the metabolism of these drugs. Moreover, there are also foods that inhibit a specific molecular species of CYP. For instance, components contained in grapefruit juice inhibit CYP3A4 and therefore, interaction resulting in elevated blood concentrations of the drugs is seen when cyclosporine and tacrolimus, midazolam, triazolam, terfenadine, etc., which are metabolized by CYP3A4, are taken with grapefruit juice.

On the other hand, it is known that there are drugs that induce drug-metabolizing enzymes. For instance, rifampicin induces CYP3A4, CYP2C9 and CYP2C19 to promote metabolism of nifedipine, warfarin, diazepam, cyclosporine, disopyramide, torbutamide, ethinyl estradiol, etc., and reduce blood concentrations.

(b) Interaction in terms of drug absorption

The route of absorption of drugs is also by the skin or oral mucosa, etc., but the main route of absorption is by the digestive tract.

Changes in gastric pH due to the effect of other drugs used concomitantly changes solubility of drugs and controls or promotes absorption from the digestive tract. For instance, gastric pH rises to 3 to 5 with administration of cimetidine during concomitant use of cimetidine and ketoconazole and as a result, there is a reduction in solubility of ketoconazole and absorption via the digestive tract is inhibited, leading to a reduction in the blood concentration.

Moreover, there are cases where when a drug is actively absorbed with concomitant drugs via the same carriers on the epithelial cells of the small intestines, absorption of the concomitant drugs is inhibited by this drug. For instance, it is reported that there is a reduction by approximately half in the cefadroxil plasma concentration when cefadroxil, a betalactam antibiotic, is concomitantly administered with cefalexine. This reduction in the blood concentration is apparently due to inhibition as a result of competition for the carrier by the two drugs.

(c) Interaction in terms of drug distribution

Drugs that have been absorbed via the digestive tract or have moved to the blood from the site of administration are distributed to blood cells at a specific ratio, or bind with proteins in plasma. The free fraction of the drug is distributed to each tissue to realize pharmacological action and therefore, when drug bound to protein is expelled from this binding site and interaction occurs so that the concentration of the free fraction of the drug rises, this pharmacological effect is enhanced. For instance, warfarin, torbutamide, etc., are released from the protein binding site, resulting in a rise in the concentration of the free fraction of the drug, when they are concomitantly used with aspirin, etc.

Moreover, P glycoproteins are found in the cells of the mucosa of the small intestines, cells of the uriniferous tubules, and endothelial cells of the capillaries of the brain, and they have the mechanism of transporting many drugs to outside the cells. When a drug that inhibits P glycoprotein is concomitantly used with a drug that is transported via P glycoprotein, there are cases where secretion of drugs into the intestines, transporting drugs out of the brain, and excretion in urine are inhibited. Vinblastin, vincristin, doxorubicin, etoposide, taxol, adriamycin, dexamethasone, hydrocortisone, verapamil, diltiazem, nifedipine, nicardipine, cyclosprin, tacrolimus, acebutolol, metoprolol, nadolol, timolol, prostaglandin, rodamine 123, digoxin, colchicine, dideoxyforscolin, etc., are drugs that are transported out by P glycoproteins. Etoposide, hydrocortisone, progesterone, testosterone, verapamil, diltiazem, nifedipine, felodipine, nitrendipine, nicardipine, cyclosporine, tacrolimus, amiodarone, lidocaine, quinidine, itraconazole, ketoconazole, erythromycin, tamoxifen, terfenadine, clorpromazine, selprolol, diprofloxacine, spironolactone are drugs that inhibit P glycoproteins ("Clinical Pharmacokinetics, Revised Version 2," Chapter II. Absorption of drugs from site of administration, page 19, Ryuichi Kato, author, Nankodo Publishers).

(d) Interaction in terms of excretion of drugs.

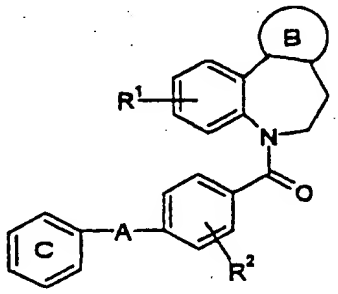
Drugs that have entered the body are excreted into the urine by the kidneys and are secreted and re-absorbed in the uriniferous tubules. Anionic carriers and cationic carriers participate in secretion from the uriniferous tubules. There is a possibility that

drugs that use the same carrier will interact with one another. Probenecid, diodrast, acetazolamide, etc., are drugs that inhibit secretion via anionic carriers. Quinine, methyl nicotinamide, trazolin *transliteration*, tetramethyl ammonium, etc., are drugs that inhibit secretion via cationic carriers.

On the other hand, when re-absorption from the uriniferous tubules is inhibited, there is an increase in the amount excreted in urine and this lowers the blood concentration. For instance, re-absorption of chlorpropamide from the uriniferous tubules is inhibited by concomitant use with sodium bicarbonate.

Consequently, there is no particular restriction to the drugs used in the present invention as long as they use the same route in terms of absorption, distribution, metabolism and excretion as other drugs or foods being used concomitantly and there is undesirable interaction in terms of pharmacokinetics. The drugs can be either the free fraction or a pharmaceutically acceptable salt. Moreover, as long as they are drugs that do not have the above-mentioned competitive relationship for the same enzyme, a combination of 2 or more types of drugs can also be used in the present invention.

Of these, nitrogenous aromatic 5-member cyclocondensed benzazepine derivatives metabolized by CYP3A4 and represented by general formula (I) or its pharmaceutically acceptable salt are ideal as the drugs used in the present invention.



(I)

The symbols in the formula are defined below:

Ring B: a nitrogenous aromatic 5-member ring, which can have substitution groups, has at least 1 nitrogen atom, and can further have 1 oxygen or sulfur atom.

R^1, R^2: amino groups that are the same or different and can be substituted with hydrogen atoms, halogen atoms or lower alkyl, lower alkyl-O-, or lower alkyl groups.

A: a single bond or group represented by the formula $-(CR^3R^4)_n-CONH-$.

n: 0 or an integer of 1 ~ 3.

R^3, R^4: the same or different hydrogen atom or lower alkyl groups (however, the R^3 and R^4 can also form a lower alkylene group with 2 ~ 7 carbons).

Ring C: benzene ring that can have substitution groups.

The nitrogenous aromatic 5-member cyclocondensed benzazepine derivatives represented by above-mentioned general formula (I) and their salts include all compounds implied by the general formula in International Kokai Patent No. 95/03305 and the definitions of the

concept of priority or choice given in the same known literature can be used for the definition of the concept of priority or choice of the present invention. That is, put simply, first "lower" means a straight or branched carbon chain with 1 to 6 carbons, and therefore, a lower alkyl group means a straight or branched C1-6 alkyl group, such as a methyl, ethyl, etc., group, a lower alkenyl group means a straight or branched C2-6 alkenyl group, such as an ethenyl, allyl, etc., group, a lower alkylene group means a straight or branched C1-6 alkylene group, such as a methylene, ethylene, etc., group, and the term lower alkenylene group means a straight or branched C2-6 alkenylene group, such as a vinylene, propenylene, etc., group.

Examples of the nitrogenous aromatic 5-member ring portion of the "nitrogenous aromatic 5-member ring, which can have substitution groups, has at least 1 nitrogen atom, and can further have 1 oxygen or sulfur atom" represented by ring B are pyrrole, pyrazole, imidazole, triazole, isoxazole, oxazole, isothiazole, thiazole, oxadiazole, and thiadiazole rings. These rings can have substitution groups, and they are condensed with the benzazepine ring at 2 adjacent ring-forming molecules.

Substitution groups that are normally used can be the substitution groups on nitrogenous aromatic 5-member ring B or on benzene ring C. Nitrogenous 5-member ring B can have 1 to 2 substitution groups and benzene ring C can have 1 to 5 (preferably 1 to 3) substitution groups. Moreover, it is preferred that the substitution groups of benzene ring C be at the o (ortho position). Examples of these substitution groups are substituted or non-substituted alkyl, alkenyl, or alkynyl groups; substituted or non-substituted cycloalkyl or cycloalkenyl groups; substituted or non-substituted aryl groups; substituted or non-substituted, saturated or unsaturated heterocyclic groups; and further, halogen atoms; hydroxyl groups, substituted or non-substituted lower alkyl-O-, lower alkenyl-O-, lower alkynyl-O-, cycloalkyl-O-, cycloalkenyl-O-, aryl-O-, aryl-lower alkyl-O-, aryl-lower alkenyl-O or aryl-lower alkynyl-O-groups; mercapto, lower alkyl-S-, lower alkenyl-S-, lower alkynyl-S-, cycloalkyl-S-, cycloalkenyl-S-, aryl-S, aryl-lower alkyl-S-, aryl-lower alkenyl-S- or aryl-lower alkynyl-S- groups; lower alkyl-O-CO-, lower alkenyl-O-CO-, lower alkynyl-O-CO-, cycloalkyl-O-CO-groups, cycloalkenyl-O-C-O-, aryl-O-CO-, aryl-lower alkyl-O-CO-, aryl-lower alkenyl-O-CO- or aryl-lower alkynyl-O-CO-groups; lower alkyl-NH-CO-; lower alkyl-CO-, lower alkenyl-CO-, lower alkynyl-CO-, aryl-CO-, lower alkyl-CO-O-, lower alkenyl-CO-O-, lower alkynyl-CO-O- or aryl-CO-O-groups; carbamoyl, carboxyl, sulfone, oxo, thioxo, cyano, nitro, amino, mono- or di-substituted amino, guanidino, amidino, and substituted or non-substituted imino groups. Bivalent groups that form a condensation ring with the benzene ring by bonding with 2 adjacent carbon atoms of the benzene ring, including hetero atoms that are substituted or non-substituted, depending on the case, such as lower alkylene, lower alkenylene, lower alkynylene, and -O-lower alkylene-O-groups can be given as the substitution groups of the benzene ring.

The substitution groups of "substituted alkyl, alkenyl, or alkynyl groups," which are the substitution groups on the above-mentioned nitrogenous aromatic 5-member ring or benzene ring, are, for instance, cycloalkyl or cycloalkenyl groups. substituted or non-substituted aryl groups; substituted or non-substituted, saturated or unsaturated heterocyclic groups; halogen atoms; hydroxyl groups, alkyl-O-, lower alkenyl-O-, lower

alkynyl-O-, cycloalkyl-O-, cycloalkenyl-O-, aryl-O-, aryl-lower alkyl-O-, aryl-lower alkenyl-O- or aryl-lower alkynyl-O- groups, mercapto, lower alkyl-S-, lower alkenyl-S-, lower alkynyl-S-, cycloalkyl-S-, cycloalkenyl-S-, aryl-S-, aryl-lower alkyl-S-, aryl-lower alkenyl-S or aryl-lower alkynyl-S- groups; lower alkyl-O-CO-, lower alkenyl-O-CO-, lower alkynyl-O-CO-, cycloalkyl-O-CO- groups, cycloalkenyl-O-CO-, aryl-O-CO-, aryl-lower alkyl-O-CO-, aryl-lower alkenyl-O-CO- or aryl-lower alkynyl-O-CO- groups; lower alkyl-NH-CO- groups; lower alkyl-CO-, lower alkenyl-CO-, aryl-CO-, lower alkyl-CO-O-, lower alkenyl-CO-O- or aryl-CO-O- groups; carbamoyl, carboxyl, sulfone, oxo, thioxo, cyano, nitro, amino, mono- or di-substituted amino, guanidino, amidino and substituted or non-substituted imino groups.

Halogen atoms and cyano, hydroxyl, carboxyl, lower alkyl-O-CO-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, phthalimide, etc., groups are given as substitution groups of "substituted alkyl-O- groups."

Lower alkyl, lower alkenyl, lower alkynyl, and lower alkyl-CO- groups are given as substitution groups of "mono- or di-substituted amino groups."

Halogen atoms, lower alkyls, lower alkenyls, lower alkynyls, lower alkyl-O-, amino, mono- or di-lower alkylamino, hydroxyl, carboxyl, etc., groups are given as substitution groups of "substituted aryl groups."

Phenyl, biphenyl, naphthyl, anthryl, fenanthryl, etc., are given as examples of "aryl groups."

Actual examples of halogen atoms are fluorine atom, chlorine atom, bromine atom, etc.

Moreover, there are cases where a salt is formed with the inorganic acid, such as hydrochloric acid, etc., organic acid, such as fumaric acid, etc., inorganic base, such as sodium, etc., and organic base, such as diethanol amine, etc., contained in the effective components of the present invention, and a salt of the above-mentioned compound that is pharmaceutically acceptable is included in the effective components of the present invention. Moreover, mixtures of each type of isomer and isolated forms of the same and water-based and solvent-based forms are all included among the effective components of the present invention. There are also compounds with multiple crystal forms among the effective components of the present invention and all of these crystal forms are implied by the present invention.

The 4'-(2-methyl-1,4,5,6-tetrahydroimidazo4,5-d1benzazepin-6-yl)carbonyl-2-phenyl benzanilide and pharmaceutically acceptable salts of the same listed in International Kokai Patent No. 94sic/03305 are given as particularly preferred examples.

These compounds can be easily obtained by the production method in above-mentioned International Kokai Patent No. 95/03305, or in accordance with this method.

There are no special restrictions to the mixture ratio of drugs used in the present invention as long as it is the amount normally used for treatment or prevention pharmacologically, but no more than 75 wt% of the total preparation is preferred, and no more than 50 wt% of the total preparation is further preferred.

A dissolving filler and, when necessary, a hydrogel-forming polymer substance, can be combined in the core containing a drug of the preparation of the present invention. In this case, the preparation of the present invention can be all but completely gelated while it is retained in the stomach of the upper digestive tract and the upper small intestines, such as the duodenum, jejunum, etc., after administration and the core itself that contains the drug is all but completely dissolved or suspended, or gelated, when a hydrogel-forming polymer substance is added, the gel layer that is produced by gelling of the outer layer is dissolved or peels off and then the drug can be released in a state that is readily absorbed (dissolved or suspended state), even in the colon of the lower digestive tract where the water content is low. Moreover, sustained release can be realized with a preparation of a hydrogel-forming polymer substance combined in the core. Consequently, drug release from the preparation is controlled and drug can be released in the ileum or colon where the amount of CYP3A4 that is distributed is low while concomitant drugs that have been simultaneously taken are being metabolized by CYP3A4 in the upper intestine, such as the duodenum, jejunum, etc., and competition for metabolism can be averted. Moreover, because preparations that are designed such that concomitant drugs will disintegrate and dissolve in the stomach are quickly metabolized in the upper small intestine, such as the duodenum, jejunum, etc., competition over metabolism by CYP3A4 with concomitant drugs can be averted, even when the drug is released in the stomach, duodenum, or jejunum after a specific time.

There are no special restrictions to the dissolving filler used in the core of the present invention as long as it is one that is usually allowed pharmaceutically and it is hydrophilic. Fillers that have the ability to retain enough water content to dissolve the drug after the filler itself dissolves and/or to adjust pH to one at which a drug will readily dissolve by dissolution of filler are examples. A filler with which the amount of water needed to dissolve 1 g of this filler is 5 mL or less, preferably 4 mL or less. The same hydrophilic bases of the present invention are examples of the former. Examples of the latter are organic acids, such as malic acid, citric acid, tartaric acid, etc. Incidentally, it is preferred that this dissolving filler be selected in accordance with the physicochemical properties of the drug. Malic acid, citric acid, sucrose, polyethylene glycol, etc., are given as said filler. Malic acid and citric acid are preferred. One filler or a mixture of 2 or more fillers can be used. When the 4'-(2-methyl-1,4,5,6-tetrahydroimidazo4,5-d1benzazepin-6-yl)carbonyl-2-phenyl benzanilide and pharmaceutically acceptable salts of the same entered in International Kokai Patent No. 94sic-03305 are used as the drugs of the present invention, malic acid and citric acid are preferred for this dissolving filler. Moreover, the dissolving capability of the drug contained in the core should be good in order to be easily absorbed the drug contained in the core in the colon where the water content is low. Methods of improving drug dissolving capability include the method whereby after dissolution of said filler, an organic acid, such as citric acid, malic acid, tartaric acid, etc., is added to bring pH to within a range at which the drug will show good solubility, the method whereby surfactant, such as polyoxyethylene hydrogenated castor oils, polyoxyethylene sorbitan higher fatty acid esters, polyoxyethylene polyoxypropylene glycols, sucrose fatty acid esters, etc., is added, the method whereby a solid dispersion with a water-soluble polymer, such as hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, polyethylene glycol, etc., or an enteric polymer, such as carboxymethyl ethyl

cellulose, hydroxypropyl methyl cellulose phthalate, methyl methacrylate-methacrylic acid copolymer, etc., the method of conversion to a soluble salt, the method whereby an inclusion complex is formed using cyclodextrin, etc. Moreover, 1 or a combination of 2 or more methods can be used as the method for improving solubility.

At least 10% of the core is the amount of dissolving filler used in the present invention.

There are no particular restrictions to the hydrogel-forming polymer substance used in the present invention as long as it is possible to control release of drugs from a pharmaceutical preparation so that the drugs can be released after a specific lag time. Examples of said polymer substance are polyethylene oxide, such as POLYOX® WSR 303 (viscosity-average molecular weight: 7,000,000, viscosity: 7,500 to 10,000 cP (aqueous 1% solution at 25°C)), POLYOX® WSR Coagulant (viscosity-average molecular weight: 5,000,000, viscosity: 5,500 to 7,500 cP (aqueous 1% solution at 25°C)), POLYOX® WSR-301 (viscosity-average molecular weight of 4,000,000, viscosity: 1650-5500 cP (aqueous 1% solution at 25°C)), POLYOX® WSR N-60K (viscosity-average molecular weight: 2,000,000, viscosity: 2,000 to 4,000 cP (2% aqueous solution at 25°C) (all made by Union Carbide), ALKOX® E-75 (viscosity-average molecular weight: 2,000,000 to 2,500,000, viscosity: 40 to 70 cP (aqueous 0.5% solution at 25°C)), ALKOX® E-100 (viscosity-average molecular weight of 2,500,000 to 3,000,000, viscosity: 90 to 110 cP (aqueous 0.5% solution at 25°C)), ALKOX® E-130 (viscosity-average molecular weight: 3,000,000 to 3,500,000, viscosity: 130 to 140 cP (aqueous 0.5% solution at 25°C)), ALKOX® E-160 (viscosity-average molecular weight: 3,600,000 to 4,000,000, viscosity: 150 to 160 cP (aqueous 0.5% solution at 25°C)), ALKOX® E-240 (viscosity average molecular weight: 4,000,000 to 5,000,000, viscosity: 200 to 240 cP (aqueous 0.5% solution at 25°C)) (all made by Meisei Kagaku Co., Ltd.), PEO-8 (viscosity-average molecular weight:1,700,000 to 2,200,000, viscosity: 20 to 70 cP (aqueous 0.5% solution at 25°C)), PEO-15 (viscosity-average molecular weight: 3,300,000 to 3,800,000, viscosity: 130 to 250 cP (aqueous 0.5% solution at 25°C)), PEO-18 (viscosity-average molecular weight: 4,300,000 to 4,800,000, viscosity: 250 to 480 cP (aqueous 0.5% solution at 25°C)) (all made by Seitetsu Kagaku Co., Ltd.), etc., hydroxypropyl methyl cellulose, such as Metolose® 90SH100000 (viscosity: 4,100 to 5,600 cP (aqueous 1% solution at 20°C), Metolose® 90SH50000 (viscosity: 2,900 to 3,900 cP (aqueous 2% solution at 20°C), Metolose® 90SH30000 (viscosity: 25,000 to 35,000 cP (aqueous 2% solution at 20°C) (all made by Shinetsu Chemical Co., Ltd.), etc., carboxymethyl cellulose sodium, such as Sunlose® F-150MC (viscosity-average molecular weight: 200,000, viscosity: 1,200 to 1,800 cP (aqueous 1% solution at 25°C)), Sunlose® F-1000MC (viscosity-average molecular weight: 420,000, viscosity: 8,000 to 12,000 cP (aqueous 1% solution at 25°C)), Sunlose® F-300MC (viscosity-average molecular weight: 300,000, viscosity: 2,500 to 3,000 cP (aqueous 1% solution at 25°C)) (all made by Nihon Seishi Co., Ltd.), etc., hydroxyethyl cellulose, such as HEC Daicel® SE850 (viscosity-average molecular weight: 1,560,000, viscosity: 2,400 to 3,000 cP (aqueous 1% solution at 25°C)), HEC Daicel® SE900 (viscosity-average molecular weight: 1,560,000, viscosity: 4,000 to 5,000 cP (aqueous 1% solution at 25°C)) (all made by Daicel Chemical Co., Ltd.), etc., and carboxyvinyl polymer, such as Carbopol 940

(viscosity-average molecular weight: approximately 2,500,000, viscosity: 100,000 cP (aqueous 2% solution at 20°C)) (B.F Goodrich Chemical Co., Ltd.), etc., and the like. Moreover, it is preferred that the polymer substance used in the present invention have a high viscosity when gelated or a high viscosity-average molecular weight. Said polymer substance is preferably, for instance, a substance that shows viscosity of 1,000 cP or higher in the form of an aqueous 1% solution (25°C) or one that shows a viscosity-average molecular weight of 2,000,000 or higher. The polymer substance of the present invention can be 1 or a combination of 2 or more with different molecular weights, grades, etc., in order to control lag time.

Incidentally, it is preferred that a light-blocking means, such as addition of a light-blocking substance or packaging, etc., be employed when polyethylene oxide is used as the hydrogel-forming polymer substance in order to prevent changes in the drug elution behavior that accompanies photodecomposition of polyethylene oxide. There are no particular restrictions to this light-blocking means as long as it has the ability to block the transmission of light. Blocking light transmission can be either absorption of light or reflection of light. There are no particular restrictions to the light-blocking substance of the present invention as long as it is usually pharmaceutically acceptable and it has the ability to block the transmission of light. Specific examples are precipitating calcium carbonate (white), shellac (pale yellowish to deep brown), magnesium carbonate (white), orange essence (pale orange to yellow), caramel (deep brown to black), medicinal carbon (black), water-soluble edible tar pigment (for instance, edible red No. 2 and No. 3, edible yellow No. 4 and No. 5, edible blue No. 1 and No. 2, etc.), natural pigment (such as β-carotene (purplish red to deep red), copper chlorophyllin sodium (bluish black to greenish black), copper chlorophyll (bluish black to greenish black), etc.), red ferric oxide (red), yellow ferric oxide (yellow), talc (white to pale gray), titanium oxide (white), lead oxide (white), cerium oxide, etc. However, it is known that the relationship between wavelength and color of the light source as well as complementary color (color that is actually seen) is colorless (complementary color; colorless) at a wavelength of 400 nm or less, purple (complementary color; yellowish green) at a wavelength of 400 to 435 nm, blue (complementary color; yellow) at a wavelength of 435 to 480, greenish blue (complementary color; orange) at a wavelength of 480 to 490, bluish green (complementary color; red) at a wavelength of 490 to 500 nm, green (complementary color; purplish red) at a wavelength of 500 to 560 nm, yellowish green (complementary color; purple) at a wavelength of 560 to 580 nm, and yellow (complementary color; blue) at a wavelength of 580 to 595 nm. A preferred light blocking substance of the present invention has, for instance, the ability to block light with a wavelength of approximately 560 nm or less. Examples of substances that block light of this wavelength are metal oxides (for instance, Mg, Mn, Fe, Co, Cu, Zn, Al, Cr, Ti, etc.) at 400 nm or less, yellow systems (yellow or yellowish green) capable of absorbing light of 400 to 480 nm, and red systems (orange or red or purplish red) capable of absorbing light of 480 to 560 nm. Moreover, ultraviolet ray blocking agents ordinarily used in the field of cosmetics can be used for an absorption wavelength of 400 nm or less. Specific examples are precipitating calcium carbonate (white), magnesium carbonate (white), orange essence (pale orange to yellow), edible pigment (such as edible red No. 2 and No. 3, edible yellow No. 4 and No. 5, etc.), natural pigment (such as β-carotene (purplish red to deep red), etc.), red ferric

oxide (red), yellow ferric oxide (yellow), zinc oxide (white), cerium oxide (yellowish green), etc. Yellow systems (for instance, yellow ferric oxide) or red systems are preferred. One or a combination of 2 or more of the light-blocking substances of the present invention can be used. Moreover, when a light-blocking substance that can generate free radicals is added, an agent that eliminates free radicals and further, a substance that enhances the effects of this eliminating agent can also be added. The term agent that eliminates free radicals here means a substance that can eliminate the above-mentioned free radicals, and there are no special restrictions as long as it is a substance with this effect. Examples are sugar alcohols such as mannitol, etc.; organic acids such as benzoic acid, etc.; tryptophan; amino acids, such as cysteine, etc.; carbonic acid ions, metal complexes, such as copper complex, manganese complex, etc.; sulfites, such as sodium hydrogen sulfite, sodium sulfite, sodium metabisulfite, etc.; thiol derivatives, such as sodium formaldehyde sulfoxylate, thioglycerol, etc.; natural resins, such as guaiac, etc.; phenol derivatives, such as nordihydroguaiaretic acid, etc.; propyl gallate, butyl hydroxyanisole, dibutylhydroxytoluene, etc.; vitamins, such as erythorbic acid, sodium erythorbate, vitamin C (for instance, the ascorbic acid esters of ascorbic acid palmitate, ascorbic acid dipalmitate, ascorbic acid stearate, etc., and the ascorbic acid salts of sodium ascorbate, calcium ascorbate, etc.), vitamin E (for instance, the tocopherol esters of dl-α-tocopherol acid succinate, d-α-tocopherol acid succinate, dl-α-tocopherol acid succinate calcium salt, dl-α-tocopherol acetate, d-α-tocopherol acetate, dl-α-tocopherol nicotinate, etc., dl-α-tocopherol, d-α-tocopherol, dl-δ-tocopherol, d-δ-tocopherol, natural vitamin E), β-carotene, etc.; peptides, such as glutathione, etc.; purine derivatives, such as uric acid, etc., and the like. One or a combination of 2 or more of these agents that eliminate free radicals can be used. Sulfites and vitamins are preferred and sodium hydrogen sulfite, ascorbic acids, sodium ascorbate sic, calcium ascorbate sic, dl-α-tocopherol and dl-α-tocopherol acetate are further preferred. Ethylenediaminetetraacetic acid or its salts, etc., can also be concomitantly used in order to enhance the effects of the agent that eliminates free radicals.

Moreover, there are no particular restrictions to the mixture ratio of the light-blocking substance as long as it is an amount with which the polyethylene oxide is usually stabilized to light. The mixture ratio varies with the type of light-blocking substance and method of its addition, but it should be 3 to 20 wt%, preferably 5 to 15 wt%, as a physical mixture in the matrix. For instance, 10 wt% or more is added with red ferric oxide and 5 to 10 wt% is added with yellow ferric oxide. If there is film coating, it is preferred that 5 to 50 wt%, particularly 10 to 20%, be adding to the film. The term "physical mixture in the matrix" used here is defined as, for instance, a means with which a drug, polyethylene oxide, and a light-blocking substance are uniformly dispersed so that the light-blocking substance is uniformly dispersed in the polyethylene oxide, which is the main base of the controlled-release preparation. Moreover, the term "film coating" means that, for instance, the light-blocking substance is dissolved or suspended in a water-soluble polymer solution, such as hydroxypropyl methyl cellulose, and tablets that have bee separately prepared are coated with a thin film of this solution. The light-blocking substance of the present invention can usually be contained anywhere in the preparation. For instance, it can be contained in the film of film coating, etc., in granules

from granulation, etc., or in the matrix (for instance, in the vicinity of the polyethylene oxide), etc.

There are no particular restrictions to the mixture ratio of the hydrogel-forming polymer substance used in the present invention as long as it is an amount with which release of the drug from the preparation usually be controlled. However, 5 to 95 wt% in terms of total preparation is preferred, and 10 to 90 wt% in terms of total preparation is further preferred. Moreover, the amount of polymer substance is preferably at least 20 mg, particularly at least 30 mg, per 1 unit preparation.

There are no particular restrictions to the hydrophilic base used in the present invention as long as it can dissolve before the above-mentioned hydrogel-forming polymer substance gels. A hydrophilic base where the amount of water needed to dissolve 1 g of this base is 5 mL or less (20 ± 5°C) is preferred. A hydrophilic base where the same is 4 mL or less (same temperature) is further preferred. Examples of this hydrophilic base are water-soluble polymers, such as polyethylene glycol (such as Macrogol 400, Macrogol 1500, Macrogol 4000, Macrogol 6000, Macrogol 20000 (all made by Nihon Yushi)), polyvinyl pyrrolidone (for instance, PVP® K30 (made by BASF), etc., sugar alcohols, such as D-sorbitol, xylitol, etc., saccharides, such as sucrose, maltose, lactulose, D-fructose, dextran (for instance, Dextran 40), glucose, etc., surfactants, such as polyoxyethylene hydrogenated castor oil (for instance, Cremophor® RH40 (made by BASF), HCO-40, HCO-60 (made by Nikko Chemicals), polyoxyethylene polyoxypropylene glycol (for instance, Pluronic® F68 (made by Asahi Denka), etc., or polyoxyethylene sorbitan higher fatty acid esters (for instance, Tween 80 (made by Kanto Chemical), etc.), etc., salts, such as sodium chloride, magnesium chloride, etc., organic acids, such as citric acid, tartaric acid, etc., amino acids, such as glycine, β-alanine, lysine hydrochloride, etc., aminosaccharides, such as meglumine, etc., and the like. Polyethylene glycol, sucrose, and polyvinyl pyrrolidone are preferred and polyethylene glycol (particularly Macrogol 6000) is further preferred. In addition, 1 or a combination of 2 or more hydrophilic bases of the present invention can be used.

When the hydrophilic base is added in the present invention, its mixture ratio is preferably 5 to 80 wt% in terms of the total preparation, particularly 5 to 70 wt% in terms of the total preparation.

There are no particular restrictions to the mixture ratio of hydrophilic base and hydrogel-forming polymer substance to core in the present invention as long as release of the drug is controlled while concomitant drugs are being metabolized by CYP3A4 enzyme in the upper small intestine, such as the duodenum. Said mixture ratio is usually 0.5 to 10 parts by weight, preferably 1 to 5 parts by weight, per 1 part by weight core. Moreover, there are no particular restrictions to the mixture ratio of hydrophilic base and hydrogel-forming polymer substance as long as release of the drug is controlled while concomitant drugs are being metabolized by CYP3A4 enzyme in the upper small intestine, such as the duodenum, etc., as previously mentioned, but it is usually 0.1 to 8 parts by weight, preferably 0.5 to 5 parts by weight, per 1 part by weight hydrogel-forming polymer substance.

The lag time until drug release can be adjusted as needed taking into consideration interaction between concomitant drugs and the drug, and it usually can be adjusted by varying the type of component and the amount of the same so that release of the drug starts between 2 to 8 hours. For instance, it can be adjusted by adjusting the amount of hydrophilic base and hydrogel-forming polymer substance added.

By means of the present invention, other additives that are acceptable in the pharmaceutical sciences can be added as needed to the core or oral pharmaceutical preparation. For instance, fillers, such as lactose, mannitol, potato starch, wheat starch, rice starch, corn starch, microcrystalline cellulose, etc., binders, such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, acacia, etc., swelling agents, such as carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose [Translator's note: Transliteration of phonetic characters] sodium, etc., lubricants, such as stearic acid, calcium stearate, magnesium stearate, talc, magnesium metasilicate, magnesium aluminate, calcium hydrogen phosphate, anhydrous calcium hydrogen phosphate, etc., fluidizers, such as hydrous silicon dioxide, light anhydrous silicic acid, dry aluminum hydroxide gel, etc., coloring agents, such as yellow ferric oxide, red ferric oxide, etc., surfactants, such as sodium lauryl sulfate, sucrose fatty acid esters, etc., coating agents, such as zein, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, etc., fragrances, such as l-menthol, mentha oil, fennel oil, etc., preservatives, such as sodium sorbate, potassium sorbate, methyl parabenzoate, ethyl parabenzoate, etc., buffers, such as citric acid, succinic acid, fumaric acid, tartaric acid, ascorbic acid or salts of the same, glutamic acid, glutamine, glycine, aspartic acid, alanine, arginine or salts of the same, magnesium oxide, zinc oxide, magnesium hydroxide, phosphoric acid, boric acid or salts of the same, etc., and the like can be added. One or a combination of 2 or more can be added as needed in an appropriate amount.

Moreover, the oral pharmaceutical preparation of the present invention can be made by conventional production methods. The method whereby the drug is mixed with each additive, such as filler, binder, lubricant, fluidizer, foaming agent, coloring agent, sweetener, etc., and when necessary, dissolving filler, and this is made into tablets as is or after being made into granules by conventional methods and sized as needed. The particles can be made by conventional dry or wet granulation. For instance, after mixing the drug and each additive, the mixture can be made into granules with a screen-type granulator, a cylindrical granulator, a tornado mill, a screw granulator, or an extrusion granulator, or powder of each component can be made into granules as is using a mixing granulator. It is also possible to make granules by the fluidized bed granulation method whereby binder solution is sprayed as it component flows through the device. Next, compression molding methods referred to as press coating or dry coating, etc., are given as methods of producing a compression coated tablet. For instance, it is possible to mix the hydrophilic base and hydrogel-forming polymer substance of the present invention, as well as filler, binder, lubricant, fluidizer, foaming agent, coloring agent, flavoring agent, sweetener, etc., as needed and then compression coat this on a core that has already been made, or make granules by conventional methods, size these granules as needed, and then mix each additive and compression coat this on the core. A compressed coating layer is ideally obtained under ordinary conditions using an ordinary tableting device for making

tablets with a core or a compression tableting device. Moreover, methods that can ordinarily be used with hydrogel preparations are mentioned as other production methods. For instance, the extrusion molding method, injection molding method, etc., can be used whereby once a core containing the drug is made, the hydrophilic base, hydrogel-forming substance and when necessary, each additive are mixed with this core, and the mixture is melted to cover the core. In addition, coating treatment such as conventional enteric coating, film coating, etc., can be performed after making tablets with a core. It is also possible to fill the tablet with a core in a capsule.

There are no particular restrictions to the method of reducing drug interaction of the present invention as long as it is a method whereby the time for which concomitant drugs and drugs coexist is varied by releasing the drugs from a preparation after a specific time lag (time control) and/or the site of absorption and metabolism is varied from that of concomitant drugs by making the preparation move to the ileum or colon, where there is little CYP3A4 and releasing the drugs from the preparation at this site while concomitant drugs are being metabolized in the upper small intestine, such as the duodenum or jejunum, etc., where a considerable amount of CYP3A4 is present (site control). For instance, the method using the preparation of the present invention can be mentioned.

Brief Description of the Drawings

Figure 1 shows the dissolution profile of Compound 1 in the preparations of Examples 1 through 3.

Figure 2 shows the results in Experiments 1 through 3, that is, the time course of the blood concentration of midazolam in each case of (1) when midazolam was orally administered singularly, (2) when Compound 1 and midazolam were orally administered simultaneously, and (3) when the preparation of Example 2 and midazolam were orally administered simultaneously.

Best Mode for Carrying out the Invention

Comparative examples, examples and test examples are given below in order to explain the present invention in further detail, but the present invention is not limited to these.

Incidentally, Compound 1 used in the following examples, etc., is 4'-(2-methyl-1,4,5,6-tetrahydroimidazo4,5-d1benzazepin-6-yl)carbonyl-2-phenyl benzanilide hydrochloride.

Example 1

One part by weight of Compound 1, 3 parts by weight of HPMC2910, and 0.5 part by weight polysorbate 80 were dissolved in 85.5 parts by weight dichloromethane-methanol mixture (8:2) and a solid dispersion was prepared by spray drying. Then 6 parts by weight malic acid were added to 9 parts by weight solid dispersion and mixed with a mortar and pestle. A core of 150 mg per tablet with a diameter of 6.5 mm was obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 50 mg polyethylene oxide (Polyox® WSR303) and 200 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer

and the compression coated tablets with a core of the present invention of 400 mg (20 mg Compound 1) per tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Example 2

One part by weight of Compound 1, 3 parts by weight of HPMC2910, and 0.5 part by weight polysorbate 80 were dissolved in 85.5 parts by weight dichloromethane-methanol mixture (8:2) and a solid dispersion was prepared by spray drying. Then 6 parts by weight malic acid were added to 9 parts by weight solid dispersion and mixed with a mortar and pestle. A core of 150 mg per tablet with a diameter of 6.5 mm was obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 62.5 mg polyethylene oxide (Polyox® WSR303) and 187.5 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer and the compression coated tablets with a core of the present invention of 400 mg (20 mg Compound 1) per tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Example 3

One part by weight of Compound 1, 3 parts by weight of HPMC2910, and 0.5 part by weight polysorbate 80 were dissolved in 85.5 parts by weight dichloromethane-methanol mixture (8:2) and a solid dispersion was prepared by spray drying. Then 6 parts by weight malic acid were added to 9 parts by weight solid dispersion and mixed with a mortar and pestle. A core of 150 mg per tablet with a diameter of 6.5 mm was obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 87.5 mg polyethylene oxide (Polyox® WSR303) and 162.5 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer and the compression coated tablets with a core of the present invention of 400 mg (20 mg Compound 1) per tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Example 4

Two parts by weight of Compound 1, 5 parts by weight malic acid and 3 parts by weight Macrogol 6000 were mixed with a mortar and pestle and a core of 100 mg per tablet with a diameter of 6 mm was obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 60 mg polyethylene oxide (Polyox® WSR303) and 140 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer and the compression coated tablets with a core of the present invention of 300 mg (20 mg Compound 1) per tablet with a diameter of 9 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Example 5

One part by weight of Compound 1, 3 parts by weight of HPMC2910, and 0.5 part by weight polysorbate 80 were dissolved in 85.5 parts by weight dichloromethane-methanol mixture (8:2) and a solid dispersion was prepared by spray drying. Then 6 parts by weight malic acid were added to 9 parts by weight solid dispersion and mixed with a mortar and pestle. A core tablet of 150 mg per tablet with a diameter of 6.5 mm was

obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 71.25 mg polyethylene oxide (Polyox® WSR303), 166.25 mg Macrogol 6000, and 12.5 mg yellow ferric oxide were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer and the compression coated tablets with a core of the present invention of 400 mg (20 mg Compound 1) per tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press.

Test Example 1

(Evaluation Method)

Screening of the dissolving filler of the present invention was conducted by the following method: One part by weight of Compound 1, 3 parts by weight of HPMC2910, and 0.5 part by weight polysorbate 80 were dissolved in 85.5 parts by weight dichloromethane-methanol mixture (8:2) and a solid dispersion was prepared by spray drying. Then 6 parts by weight of each filler were added to 9 parts by weight solid dispersion and mixed with a mortar and pestle. A core tablet of 150 mg per tablet with a diameter of 6.5 mm was obtained under tableting pressure of 500 kg/punch using an oil press. Separately, 75 mg polyethylene oxide (Polyox® WSR303) and 175 mg Macrogol 6000 were mixed with a mortar and pestle as the outer layer. The core was placed in the center of the outer layer and the compression coated tablets with a core of the present invention of 400 mg (20 mg Compound 1) per tablet with a diameter of 9.5 mm were made under a tableting pressure of 1,000 kg/punch using an oil press. This tablet was immersed for 3 hours in water at 37°C and then the gelated part of the tablet was peeled off and the undissolved core was removed. The core was dried in a dryer overnight at 40°C and then weighed. The percentage that had dissolved was calculated from the dry weight and initial weight.

(Results and Discussion)

The screening results are shown in Table 1. The results of the test indicate that when citric acid or malic acid was used, dissolving performance was high. Dissolving performance of Compound 1 is dependent on pH and increases in the region of a low pH and it therefore appears that this result is due to the hydrophilic property and the fact that pH was kept low after dissolution.

(Table 1)

Filler	Dissolved percentage (%)
Citric acid	65
Malic acid	79

Test Example 2

Dissolution tests were performed on the preparations in Examples 1 through 3. The tests were conducted by the Second Dissolution Testing Method (Paddle Method) of the Pharmacopoeia of Japan (paddle rotation: 200 rpm) using 500 ml of 1st fluid of the Disintegration Testing Method of the Pharmacopoeia of Japan as the dissolution medium.

Sampling was performed each hour and the amount of Compound 1 in the sampled solution was determined by the UV method.

(Results)

The results of the Dissolution tests are shown in Figure 1. The figure confirms that Compound 1 is first released from the preparation of the present invention after a specific amount of time. Moreover, the results show that the lag time until release starts can be adjusted by adjusting the mixture ratio of the polyethylene glycol and polyethylene oxide.

Test Example 3

The following test was conducted using midazolam as the concomitant drug metabolized by CYP3A4:

(Preparation of Sample Solution)

(1) Aqueous solution for oral administration containing midazolam: After preparing commercial midazolam injectable liquid (brand name: Dormicum® injection, made by Roche Co., Ltd., marketed by Yamanouchi Seiyaku) to a concentration of 0.2 mg/ml with aqueous hydrochloric acid solution (pH of 3), HPMC2910 was added at 3-times the amount of midazolam to obtain a liquid for oral administration.

(2) Aqueous solution for oral administration containing Compound 1: Compound 1 was dissolved to a concentration of 0.5 mg/ml with an aqueous hydrochloric acid solution (pH of 3) to obtain a liquid for oral administration.

(Experiment 1)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the aqueous solution for oral administration containing midazolam using a catheter for oral administration (4 mg/dog). After administration, blood was collected from the veins of the front legs and the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Experiment 2)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the aqueous solution for oral administration containing Compound 1 (10 mg/dog). Thirty minutes after administration the the aqueous solution for oral administration containing midazolam was orally administered using a catheter for oral administration (4 mg/dog). After midazolam administration, blood was collected from the veins of the front legs and the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Experiment 3)

Male beagle dogs (n = 6) that had been fasted for approximately 20 hours were orally administered the preparation of Example 2 (20 mg/dog) with 30 ml of water. Thirty minutes after administration an aqueous solution for oral administration containing midazolam (4 mg/dog) was orally administered using a catheter for oral administration. After midazolam administration, blood was collected from the veins of the front legs and

the plasma concentration of midazolam was determined by the HPLC/UV method over time.

(Results and Discussion)

As is clear from the results of Experiments 1 and 2, when the aqueous solution for oral administration containing Compound 1 was concomitantly used by oral administration before oral administration of the midazolam, significant changes were seen in that there was significant elevation of the midazolam blood concentration and the area under concentration (AUC) curve increased by at least 2-fold, etc., when compared to singular oral administration of midazolam (Figure 2 and Table 2). The reason for this apparently is that Compound 1, which has the same route of metabolism by CYP3A4 inhibits metabolism of midazolam in the small intestine and as a result, there is a an increase in the midazolam blood concentration and AUC.

Table 2. AUC of midazolam plasma concentration

	AUC (ng · h/ml)
Experiment 1 (Midazolam singular administration)	9.0 ± 6.0
Experiment 2 (Concomitant use of aqueous solution for oral administration containing Compound 1)	21.2 ± 8.5*
Experiment 3 (Concomitant use of preparation of Example 2)	10.9 ± 7.3

*$p < 0.05$ (to Experiment 1)

On the other hand, as is clear from the results of Experiment 1 and Experiment 3 when the preparation of Example 2 was concomitantly used by oral administration before oral administration of the midazolam, the midazolam blood concentration and AUC showed almost the same result as with midazolam singular administration (Figure 2 and Table 2). From this finding it appears that by means of the preparation of the present invention, metabolism of the midazolam by CYP3A4 in the small intestine is not inhibited by Compound 1 because Compound 1 is released after the midazolam has been metabolized by CYP3A4 in the upper small intestine and as a result, there is no effect on the midazolam blood concentration or AUC. Moreover, it was confirmed that the blood concentration of Compound 1 was enough to provide pharmacologically the therapeutic or prophylactic effect of Compound 1 once the midazolam had cleared from the blood.

Based on the above-mentioned, it was confirmed that undesirable effects of drugs on the blood concentration of other drugs being used concomitantly when drugs and other drugs being used concomitantly are metabolized by the drug-metabolizing enzyme CYP3A4 can be averted by the preparation of the present invention.

Industrial Applicability

The oral pharmaceutical preparation of the present invention can reduce interaction between drugs and concomitant drugs because competition over metabolism in the epithelial cells of the small intestine can be reduced, or the time for which drugs that have been absorbed *in vivo* (intravascularly) and concomitant drugs coexist in the

liver can be varied by releasing the drugs after a specific lag time in order to vary the time when the concomitant drugs and drugs coexist (time control) and/or by making the preparation move to the ileum or colon, where there is little CYP3A4, and releasing the drugs at this site so that the site of absorption or metabolism is different from that of concomitant drugs (site control).

When the oral pharmaceutical preparation of the present invention absorbs the water content while in the stomach or duodenum, the core itself almost simultaneously is dissolved and suspend or gelated. As a result, drug is released into the ileum or colon where there is little CYP3A4, making it possible to avert metabolism by CYP3A in the digestive tract and to absorb the drug *in vivo*. By administering the preparation of the present invention, it is possible to control changes in the blood concentration of concomitant drugs. Moreover, by varying the absorption time of concomitant drugs and drugs contained in the preparation of the present invention, it is possible to vary the time for which the drugs and concomitant drugs coexist in the liver and therefore, a reduction in drug interaction in the liver can be expected with the preparation of the present invention.

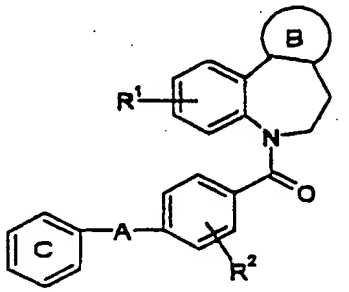
Claims

1. An oral pharmaceutical preparation, which contains a core containing a drug, a hydrophilic base, and a hydrogel-forming polymer substance.

2. The oral preparation according to Claim 1, wherein the drug is metabolized by cytochrome P-450.

3. The oral preparation according to Claim 1 or Claim 2, wherein the drug is metabolized by CYP3A4.

4. The oral pharmaceutical preparation according to any one of Claims 1 through 3, wherein the drug is a nitrogenous aromatic 5-member cyclocondensed benzazepine derivative represented by general formula (I) or a pharmaceutically acceptable salt of the same.



(I)

The symbols in the formula are defined below:

Ring B: a nitrogenous aromatic 5-member ring, which can have substitution groups, has at least 1 nitrogen atom, and can further have 1 oxygen or sulfur atom.

R^1, R^2: amino groups that are the same or different and can be substituted with hydrogen atoms, halogen atoms or lower alkyl, lower alkyl-O-, or lower alkyl groups.

A: a single bond or group represented by the formula $-(CR^3R^4)_n-CONH-$.

n: 0 or an integer of 1 ~ 3.

R^3, R^4: the same or different hydrogen atom or lower alkyl groups (however, the R^3 and R^4 can also form a lower alkylene group with 2 ~ 7 carbons).

Ring C: benzene ring that can have substitution groups.

5. The oral pharmaceutical preparation according to Claim 4, wherein the drug is 4'-(2-methyl-1,4,5,6-tetrahydroimidazo4,5-d 1benzazepin-6-yl)carbonyl-2-phenyl benzanilide or a salt of the same.

6. The oral pharmaceutical preparation according to any one of Claims 1 through 5, wherein the core contains a dissolving filler.

7. The oral preparation according to Claim 6, wherein once water has penetrated the core, the dissolving filler can dissolve or suspend the drug.

8. The oral preparation according to Claim 7, wherein the dissolving filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, polyethylene glycol, and sucrose.

9. The oral pharmaceutical preparation according to Claim 8, wherein the dissolving filler is malic acid.

10. The oral pharmaceutical preparation according to any one of Claims 1 through 9, wherein the hydrophilic base is 1 or 2 or more with a solubility of the amount of water necessary to dissolve 1 g of base being 5 mL or less.

11. The oral pharmaceutical preparation according to Claim 10, wherein the hydrophilic base is 1 or 2 or more having a solubility of the amount of water necessary to dissolve 1 g of base being 4 mL or less.

12. The oral pharmaceutical preparation according to Claim 10, wherein the hydrophilic base is 1 or 2 or more selected from the group consisting of polyethylene glycol, polyvinyl pyrrolidone, D-sorbitol, xylitol, sucrose, maltose, lactulose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine.

13. The oral pharmaceutical preparation according to Claim 12, wherein the hydrophilic base is polyethylene glycol, sucrose, or polyvinyl pyrrolidone.

14. The oral pharmaceutical preparation according to any one of Claims 1 through 13, wherein the hydrogel-forming polymer substance is 1 or 2 or more whose average molecular weight is 2,000,000 or more and/or whose viscosity of an aqueous 1% solution (25°C) is 1,000 cP or higher.

15. The oral pharmaceutical preparation according to Claim 14, wherein the hydrogel-forming polymer substance is 1 or 2 or more selected from the group consisting of polyethylene oxide, hydroxypropyl methyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and carboxyvinyl polymer.

16. The oral pharmaceutical preparation according to any one of Claims 1 through 15, wherein the hydrogel-forming polymer substance contains at least 1 type of polyethylene oxide.

17. The oral pharmaceutical preparation according to Claim 16, which further contains a light-blocking substance.

18. The oral pharmaceutical preparation according to Claim 17, wherein the light-blocking substance is selected from the group consisting of precipitated calcium carbonate, medicinal carbon, magnesium carbonate, edible pigment, red ferric oxide, and yellow ferric oxide.

19. The oral pharmaceutical preparation according to Claim 18, wherein the light-blocking substance is yellow ferric oxide.

20. A method of reducing undesirable interaction between drugs and concomitant drugs that use the same route in terms of *in vivo* drug absorption, distribution, metabolism, or excretion using an oral pharmaceutical preparation according to any one of Claims 1 through 19.

21. The method according to Claim 20, wherein the drug interaction is competition for metabolism by CYP3A4.

Abstract

The present invention pertains to an oral preparation with which undesirable interaction between multiple drugs that use the same route as concomitant drugs in terms of absorption, distribution, metabolism, or excretion is reduced and a method thereof.

The oral pharmaceutical preparation of the present invention contains a core containing a drug, a hydrophilic base, and a hydrogel-forming polymer substance. Competition over metabolism in the epithelial cells of the small intestine can be reduced, or the time for which drugs that have been absorbed *in vivo* (intravascularly) and concomitant drugs coexist in the liver can be varied by releasing the drugs after a specific lag time in order to vary the time when the concomitant drugs and drugs coexist (time control) and/or by making the preparation move to the ileum or colon, where there is little CYP3A4, and releasing the drugs at this site so that the site of absorption or metabolism is different from that of concomitant drugs (site control).

Translator's note: Followings are transliteration of phonetic characters

N-propylazimalin, nisergolin, trifluperiol, brofalomin, amiframine, banrafaxin, tomoxetin, anfentanyl, conivaptan, trazolin, croscarmellose (sodium)

Figure 1

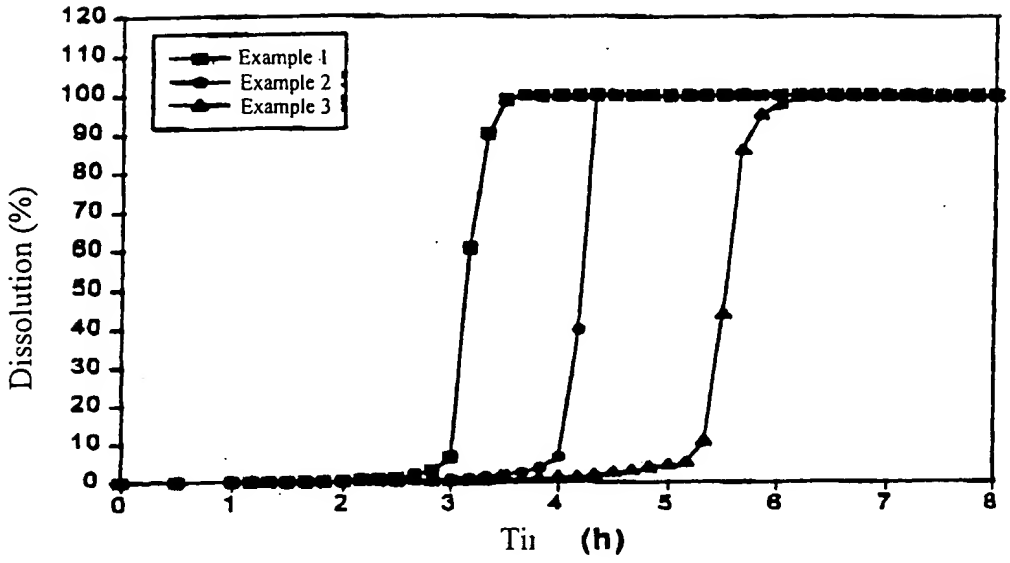


Figure 2